IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Robert C. Spiro et al. Attorney Docket No.: DEPYP015

Application No.: 09/652,604 Examiner: Laurie Mayes

Filed: August 30, 2000 Group: 1653

Title: COLLAGEN/POLYSACCHARIDE BILAYER MATRIX

CERTIFICATE OF MAILING
I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as first-class mail on June 25, 2003 in an envelope addressed to mail Stop 1653. Commissioner for Patents, P.O. Box 1450 Alexandria, VA 22313-1450.

Signed Natalie Morgan
Natalie Morgan

RESPONSE TO OFFICE ACTION

Mail Stop 1653
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is in response to the Office Action of December 31, 2002. A Request for Extension of Time accompanies this Response with the appropriate fee. With the Extension the Response is due on June 30, 2003.

The finality of the Restriction Requirement is acknowledged. Applicants have previously canceled claims directed to the non-elected inventions.

Claims 1, 2, 4-6, 8, 10 and 15 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by *Cook et al.* (U.S. Pat. No. 5,916,585), of record. This rejection is respectfully traversed. The Examiner states that *Cook et al.* teach a biodegradable matrix comprised of two layers, citing col. 5, lines 30-45.

According to that passage, the first layer is a biodegradable support member which is hydrophobic. See col. 9, lines 54 to col. 10, line 22. This first layer, however, is not cross-linked, as required by the present claims. This support layer is then linked to a first hydrophilic polymer layer by cross-linking. This first hydrophilic layer may be cross-linked. (See Item 14 in Fig. 1, Item 24 in Fig. 2, Item 34 in Fig. 3, Item 44 in Figs. 4a, 4b and 4c,

Item 54 in Fig. 5 and Item 62 in Fig. 6.) A second layer of hydrophilic polymers may be bonded to the first layer. (See Item 38 in Fig. 3, Item 46 in Fig. 4c, Item 58 in Fig. 5 and items 64 and 66 in Fig. 6.) Then spacers and/or bioactive species may be attached to the outermost hydrophilic layer. However, none of the additional hydrophilic layers is cross-linked. Therefore, as exemplified in Figs. 1-6, there can only be one cross-linked layer in the matrix, i.e., Items 14, 24, 34, 44, 54 and 62. All of the other layers are un-cross-linked. Accordingly, *Cook et al.* does not disclose a multi-layer biodegradable matrix comprising two layers, each of said layers comprising a cross-linked polymeric component selected from a group consisting of a protein and a polysaccharide. Accordingly, it is submitted that *Cook et al.* does not anticipate any of the claims, and withdrawal of the rejection is requested.

Claims 1, 2 and 5 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by *Schwartz et al.* (U.S. Pat. No. 5,906,997), of record. This rejection is respectfully traversed. The Examiner states that *Schwartz et al.* teach a biodegradable multi-layer cross-linked matrix comprised of a polysaccharide chitin, chitostan, hyaluronic acid, heparin, heparan sulfate and chondroitin sulfate. This rejection is respectfully traversed. *Schwartz et al.* do not appear to make a multi-layer matrix. A membrane is made from a solution of a polyether and a carboxypolysaccharide. The solution of the two components is poured onto a flat surface and permitted to dry to form a membrane. The association of the two components is apparently accomplished through hydrogen bonding. (See col. 5, lines 45-49.) Therefore, *Schwartz et al.* teaches only a single layer, and moreover, that single layer contains neither a cross-linked protein nor a cross-linked polysaccharide. The carboxypolysaccharide component of the membrane in *Schwartz et al.* is associated with a polyether, but is not cross-linked. Accordingly, it is submitted that *Schwartz et al.* does not anticipate the claims, and this rejection should be withdrawn.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by *Hubbell et al.* (U.S. Pat. No. 5,573,934), of record. The Examiner states that *Hubbell et al.* teach a polymer comprising layers comprised of alginate, hyaluronic acid or several other materials in a covalently-bonded, cross-linked polymeric network, citing col. 12, lines 6-9. However, the passage cited by the Examiner does not appear to support a multi-layer structure. The passage at col. 16, lines 31-33 indicates that rather than using the material to form thin intravascular coatings, the material may be used to form thicker layers of gel. Accordingly, *Hubbell et al.* does not disclose a multi-layer biodegradable matrix and do not anticipate the claims. It is respectfully requested that this rejection be withdrawn.

Claims 1-6, 8, 10, 11, 13, 15 and 16 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by *Yannas* (U.S. Pat. No. 4,902,289), of record. The Examiner states that *Yannas* teaches a multi-layer matrix comprising two layers comprised of covalent cross-linked collagen and where the polysaccharide for both layers is selected from any of several polysaccharides. This rejection is respectfully traversed. *Yannas* discloses a multi-layer blood vessel prosthesis wherein an inner layer is a cross-linked aminopolysaccharide and the outer layer is a cross-linked collagen-aminopolysaccharide polymer. The second layer is formed on the first layer by freeze drying. The layers may also be formed of a synthetic material such as polyhydroxyacetic ester. The polyhydroxyacetic ester is neither a protein nor a polysaccharide. The collagen-aminopolysaccharide polymer layer is made from a material disclosed in another Yannas patent, U.S. Pat. No. 4,280,954, copy enclosed. This is cited in *Yannas* at col. 3, lines 8-12. However, the collagen-aminopolysaccharide layer is not a protein cross-linked to a polysaccharide. As an example of such material, the Examiner is invited to review Example 2 in the *Yannas* Pat. No. 4,280,954. The collagen is mixed with the polysaccharide, which causes collagen to co-precipitate, forming a tangled mass of collagen fibrils coated with the polysaccharide which somewhat resembles a tangled ball of yarn. (See col. 13, lines 11-19.) This mass can be dried and covalently cross-linked. (See Example 4 in U.S. Pat. No. 4,280,954.) However, this forms a material which is a mass of collagen coated with cross-linked polysaccharide, not a polysaccharide cross-linked to collagen. Therefore, no layer disclosed in the *Yannas* Pat. No. 4,902,289 is a cross-linked protein or a cross-linked polysaccharide. Morever, Yannas is directed to a blood vessel prosthesis, the purpose of which is to contain blood and exclude tissue. The materials of the invention herein are directed to tissue in-growth for tissue regeneration. Accordingly, it is submitted that *Yannas* 4,902,289 does not anticipate the present claims, and withdrawal of the rejection is requested.

Claims 1, 6 and 18 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by *Boyce* (U.S. Pat. No. 5,273,900), of record. The Examiner states that *Boyce* teaches a cross-linked dermal membrane comprising collagen and chondroitin sulfate where said layers are chemically cross-linked to each other with glutaraldehyde and are also cross-linked by thermal dehydration. This rejection is respectfully traversed. The first layer of the dermal membrane is made from a solution of collagen and a GAG, which is frozen, lyophilized and then cross-linked. (See col. 7, lines7-16 and lines 40-45.) A second layer is added to the first layer. The second layer is also formed from a solution of collagen and GAG, then cross-

linked. (See col. 7, lines 45-60.) However, neither of these layers is a cross-linked protein or cross-linked polysaccharide. They are layers comprising a protein cross-linked to a polysaccharide. Accordingly, *Boyce* does not teach a multi-layer biodegradable matrix comprising two layers, each of said layers comprising a cross-linked protein or a cross-linked polysaccharide. Accordingly, withdrawal of this rejection is respectfully requested.

Cols. 1-6, 8, 9, 12, 14, 15, 16 and 17 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over *Höök et al.* (U.S. Pat. No. 4,784,989) and *Liu et al.* (U.S. Pat. No. 5,972,385), in view of *Schwartz et al.*, all of record. The Examiner states that *Höök et al.* teach a cross-linked polymeric component comprising fibrinogen, fibronectin, albumin, collage, laminen, dextran or alginate where the cross-linking agent is divinyl sulfone. The Examiner further states that *Liu et al.* teach a cross-linked polymeric component comprising hyaluronic acid, chondroitin sulfate, dermatan sulfate, keratan sulfate, heparin, heparan sulfate, dextran, dextran sulfate, alginate or collagen and/or fibrinogen. The Examiner relies on *Schwartz et al.* to teach the advantages of using a multi-layered matrix to manipulate the components and ingredients in a layer resulting in each layer exhibiting different properties. The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time of the invention was made by Applicant to add a second layer comprising the proteins and polysaccharides listed above by *Höök* or *Liu*, of either the same components as the first layer or different components from the lists above yielding a second layer of different composition and density, and which is cross-linked with divinyl sulfone, in order to be able to manipulate the components and concentrations of each layer to yield more control and flexibility of the properties exhibited. This rejection is respectfully traversed. *Höök* teaches a use of a un-cross-linked protein, such as collagen, optionally bound to a carrier gel, such as Sepharose, applied to the skin, dried and removed. Certain micro-organisms on the skin adhere to the layer of protein and are removed from the skin when the layer is peeled off. Not only is the protein layer un-cross-linked, but it has nothing to do with tissue regeneration.

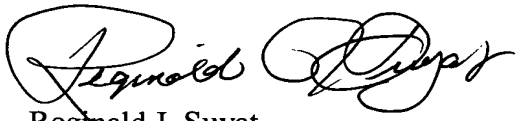
Liu et al. teaches a single layer of a matrix of a polysaccharide cross-linked to collagen. The Examiner has stated that neither *Liu et al.* nor *Höök et al.* teaches a multi-layered matrix for use in tissue regeneration. The Examiner relies on *Schwartz et al.* to teach advantages of using a multi-layered matrix to manipulate the components and ingredients in each layer, resulting in each layer exhibiting different properties as desired. However, it is submitted that it is not the motivation that one of ordinary skill in the art would gain from reading *Schwartz et al.* *Schwartz et al.* has two layers because apparently the invention will

not work without those two layers. First, the two layers must be sufficiently bonded together; otherwise there is insufficient structural integrity. (See col. 6, lines 1-3.) The polyether layer must be present to provide flexibility (col. 7) and antithrombogenicity. (See col. 7, lines 12-32.) The carboxypolysaccharide layer is provided for bioadhesiveness. Thus, without one of these layers the improvements achieved by the invention in *Schwartz et al.*, are not attained. However, there is no feature of the *Höök et al.* or *Liu et al.* devices, which is apparently lacking and for which one would look to *Schwartz et al.* to remedy. Stiffness, antithrombogenicity and bioadhesiveness to the extent they are necessary, do not appear to be insufficient in the devices in *Höök et al.* and *Liu et al. Höök's* membranes are removed from the skin after 20 to 30 minutes with a scalpel. There does not appear to be any reason to modify *Höök's* membranes with a second layer to impart another desirable property not already present in the single layer. The same applies for the device disclosed in *Liu.* Although one might assume that antithrombogenicity is a desirable property in *Liu's* materials, there is no teaching that this property is insufficient or lacking in *Liu's* device. Accordingly, using the teachings of *Schwartz et al.*, there is no reason to modify the devices of either of the primary references. Accordingly, it is submitted that one of ordinary skill in the art would not be led to modify the devices of the prior references as suggested by the Examiner from the teachings of *Schwartz et al.*. The claims are submitted to be unobvious over the combination of *Höök et al.*, *Liu et al.* and *Schwartz et al.* For these reasons, it is submitted that this rejection should be reconsidered and withdrawn.

It is submitted that the application is in condition for allowance, and passage to issuance is respectfully requested.

Respectfully submitted,

BEYER WEAVER & THOMAS, LLP



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